

The University of Chicago

THE EFFECT ON THE FETUS OF
PENTOBARBITAL SODIUM AND
PENTOTHAL SODIUM

PART OF A DISSERTATION SUBMITTED TO THE FACULTY OF THE
DIVISION OF THE PHYSICAL SCIENCES IN CANDIDACY
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHARMACOLOGY

1942

By

ROBERT DREISBACH

Reprinted from
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Vol. 79, No. 3
1943

The University of Chicago

THE EFFECT ON THE FETUS OF
PENTOBARBITAL SODIUM AND
PENTOTHAL SODIUM

PART OF A DISSERTATION SUBMITTED TO THE FACULTY OF THE
DIVISION OF THE PHYSICAL SCIENCES IN CANDIDACY
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHARMACOLOGY
1942

By
ROBERT DREISBACH

Reprinted from
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Vol. 79, No. 3
1943



THE EFFECT ON THE FETUS OF PENTOBARBITAL SODIUM AND PENTOTHAL SODIUM

ROBERT DREISBACH¹

*From the Department of Pharmacology, University of Chicago,
Chicago, Illinois*

Received for publication August 2, 1943

Pentobarbital sodium and pentothal sodium find such extensive use in obstetrical practice that it is desirable to determine their effects on the fetus. The experiments reported here were undertaken to study the effects of these drugs on the respiration of the rabbit fetus, and to ascertain whether the effects are direct or are due to changes in oxygen saturation in the blood.

METHOD AND MATERIAL. Rabbits were prepared for observation of fetal respiration by the technique of Rosenfeld and Snyder (6). The respiratory movements of the fetuses were observed directly through the wall of the uterus following laparotomy carried out beneath the surface of a saline bath. The barbiturates were injected into the maternal ear vein at the rate of 1 cc. per minute, using a 5% solution in distilled water.

In 8 litters, in which the depressant effect of pentobarbital sodium was studied, 21 fetuses were observed and 43 living fetuses were delivered at the end of the experiments. In 8 other litters, in which the effect of pentothal sodium was investigated, 20 fetuses were observed and 51 living fetuses were delivered.

OBSERVATIONS. 1. *Pentobarbital sodium.* Direct observation of full-term fetuses within the intact uterus revealed a striking effect upon fetal respiratory movements following the administration of pentobarbital sodium to the maternal animal. Depression or disappearance of respiratory movements was regularly noted. Furthermore, the magnitude of the decrease in rate of respiration and the duration of effect were related to the quantity of the drug which had been administered. At a dosage level of 20 mg./kg. maternal body weight, the depression of fetal respiration was marked, falling to one-third or less of the initial rate, and usually persisted longer than one-half hour. With 10 mg./kg. a decrease in fetal respiratory rate occurred but did not approach the level of apnea. Usually within fifteen minutes the rate returned to normal. After 5 mg./kg. the decrease was smaller and less prolonged than that following 10 mg./kg. In addition to the immediate response of the fetuses, it was evident that preceding doses, even of 5 mg./kg., influenced the amount and duration of the depression of fetal respiratory activity which followed subsequent injections. Thus, in rabbit 307, fetal apnea followed a total dose of 20 mg./kg. (fig. 1). An initial dose of 5 mg./kg. resulted in a definite decrease in respiratory rate and, likewise, a second injection of 5 mg./kg. slowed respiration. The duration of the respiratory depression was about ten minutes. An additional 10 mg./kg. dose, injected an hour later, resulted in fetal apnea and a slower rate of fetal respiration in the subsequent hour than in the

¹ Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the University of Chicago.

preceding one, thus indicating a cumulative effect of the previous injections. The maternal animal showed a little analgesia following 10 mg./kg., although the respiratory rate was diminished. After 20 mg./kg., the respiratory rate was considerably slower and the response to nasal stimulation was sluggish, although the conjunctival reflex remained active.

In table 1 are recorded the results of experiments in 8 litters of rabbits in which fetal respiratory activity continued throughout a period of 100 to 200 minutes. Doses of 5 or 10 mg./kg. of pentobarbital sodium were injected into the maternal ear vein at various intervals, usually about 20 minutes apart. Under these conditions, it was found that at a dosage level of 20 mg./kg. fetal respiration was decreased below a level of one-third of the rate which preceded injection, and the duration of depression was usually thirty minutes or longer.

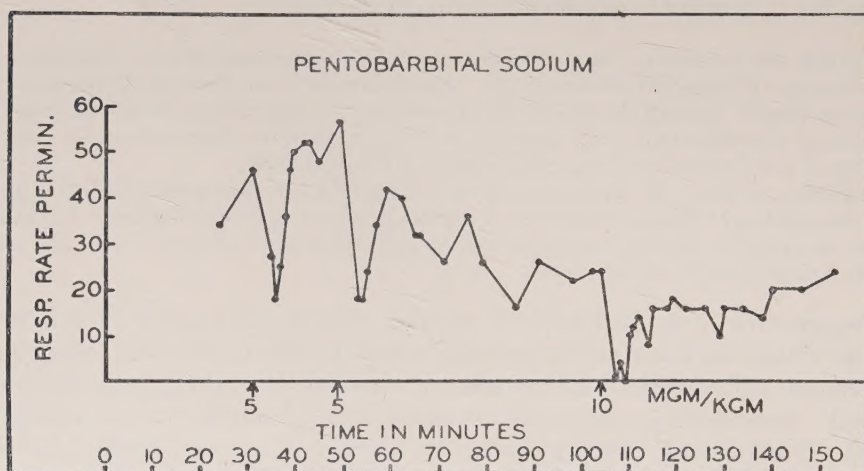


FIG. 1. The effect upon fetal respiratory activity of pentobarbital sodium showing that depression deepens as total dosage rises. Intravenous injection into maternal animal at full-term at rate of 17 mg./kg. per minute. Rabbit No. 307.

The total dosage of pentobarbital sodium during an entire experiment did not exceed 30 mg./kg. At this dosage level, rhythmical fetal respiration was markedly depressed or abolished, and this effect persisted until the end of the experiment. The maternal animal showed slightly greater depression than after a 20 mg./kg. dose.

2. *Pentothal sodium.* Observation of the effect of pentothal sodium on the fetus afforded additional evidence of the striking depression of fetal respiratory activity following the administration of a barbiturate, although pentothal sodium is inactivated by the body more rapidly than pentobarbital sodium. In a typical experiment (fig. 2, rabbit 41), it was evident that following pentothal sodium the rate of fetal respiration was markedly decreased, but the duration of depression was briefer than in the case of pentobarbital sodium. About five minutes following the injection of the second and third doses of 10 mg./kg. each, respiratory movements had reached the pre-injection level. Despite the ad-

ministration of a total of 45 mg./kg. of pentothal sodium within an hour, rhythmic respiratory movements persisted at the end of the experimental period of

TABLE 1

Effect of pentobarbital sodium on intrauterine respiration

A single fetus of a litter was selected for tabulation of the record of changes of respiratory rate.

RABBIT NUMBER	TIME OF IN- JECTION OF MATERNAL ANIMAL (MIN. AFTER LAPAROTOMY)	DOSAGE OF PENTOBARBI- TAL SODIUM INTRA- VENOUSLY	FETAL RESPIRATION BEFORE INJECTION	FETAL RESPIRATION AFTER INJECTION	DURATION OF RESPIRATORY DEPRESSION	DEPRESSANT DOSE (RESP. DECREASED TO ½ INITIAL RATE)	DURATION OF EXPERIMENT
		mg./kg.			min.	mg./kg.	min.
307	34	5	40	20		20	160
	52	5	50	20			
	106	10	25	5	30		
463	21	10	45	5	40	10	180
	122	10	25	5	50		
300	22	5	50	30		20	120
	33	5	45	30			
	48	10	25	5	10		
	72	5	30	5	50		
382	15	10	40	25		20	200
	37	10	60	20	40		
	88	10	10	0	40		
604	19	10	35	25		30	130
	35	5	25	10			
	59	5	20	15			
	82	5	25	10			
	90	5	25	5	30		
710	19	5	20	15		20	140
	29	5	10	10			
	39	5	15	10			
	49	5	15	5	30		
	84	5	5	0	25		
812	13	10	30	15		20	120
	34	10	20	5	30		
	64	10	35	15	40		
733	19	10	30	15		20	110
	37	10	20	5	10		
	62	10	20	5	40		

one and one-half hours. The maternal animal showed little or no analgesia at the end of the experiment. However, immediately following injection at the level of

20, 30 and 45 mg./kg., this animal showed marked slowing of respiration, and definite analgesia was revealed by sluggish response to nasal and conjunctival stimulation. After five minutes, depression of the maternal animal had largely disappeared.

Table 2 records the results of experiments with 8 litters in which intra-uterine respiratory activity continued for periods of 120 to 270 minutes. During this time the influence on the fetus of the various amounts of pentothal sodium was observed. Pentothal sodium, in single doses of 2.5 to 15 mg./kg. maternal body weight, was injected into the maternal ear vein at intervals of about fifteen minutes. Under these conditions it was found that a single injection of 10 mg./kg. of pentothal sodium decreased fetal respiratory activity, the rate being lowered usually below a level of one-third that of the initial rate. Recovery required five to ten minutes. No marked analgesia of the maternal animal was

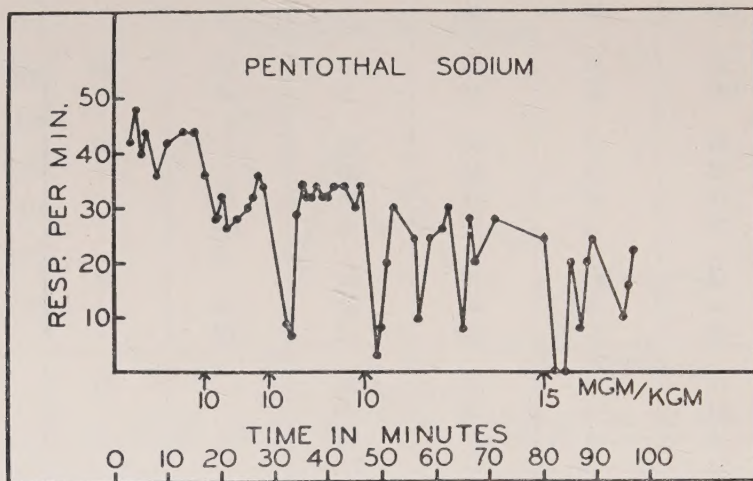


FIG. 2. The effect upon fetal respiratory activity of pentothal sodium showing that depression is brief and the cumulative effect is relatively small. Intravenous injection of the maternal animal at full-term at rate of 17 mg./kg. per minute. Rabbit No. 41.

noted following a single dose of 10 mg./kg. of pentothal sodium, although the respiratory rate was diminished.

The total dosages in various animals ranged from 30 to 55 mg./kg. during an experiment. There was evidence of relatively little cumulative effect of pentothal sodium upon the fetuses in contrast to that of pentobarbital sodium. At the end of an experiment, the fetal respiratory rate remained within normal limits. The outstanding feature was the brief duration of the depression of fetal respiration.

3. *The oxygenation and carbon dioxide content of fetal blood during apnea following the administration of pentothal sodium.* The occurrence of apnea in the fetus, despite the persistence of normal respiration in the maternal animal following administration of barbiturates, afforded a favorable opportunity to determine whether or not the oxygen and carbon dioxide content of the fetal blood remained

TABLE 2

Effect of pentothal sodium on intrauterine respiration

RABBIT NUMBER	DEPRESSANT DOSE (RESP. DECREASED TO $\frac{1}{2}$ INITIAL RATE)	FETAL RESPIRATION AT BEGINNING	FETAL RESPIRATION AFTER FIRST DEPRESSANT DOSE	DURATION OF RESPIRATORY DEPRESSION	TOTAL DOSE OF PENTOTHAL SODIUM GIVEN MATERNAL ANIMAL INTRA- VENOUSLY	NUMBER OF DOSES	DURATION OF EXPERIMENT
	mg./kg.			min.	mg./kg.		min.
413	15	25	0	5	40	7	170
459	25	70	20	5	45	6	130
41	20	45	10	5	45	4	120
439	10	35	5	10	55	5	120
467	5	20	5	5	30	6	170
753	10	35	5	5	40	4	170
453	10	25	5	10	30	6	150
431	5	40	5	5	30	12	280

TABLE 3

Fetal blood oxygen and carbon dioxide during anesthetic apnea

RABBIT	FETUS NUMBER	TIME	RESPIRA- TORY RATE	OXYGEN CAPACITY	OXYGEN CONTENT	OXYGEN SATURA- TION	CARBON DIOXIDE CONTENT	DOSE OF PENTOTHAL TO MATERNAL ANIMAL I.V.
		minutes		vol. %	vol. %	%		mg./kg.
516	F ₁	0	86	13	11	85	51	15
		23*						
	F ₁	27	0	12	11	92	42	
	F ₁	50	72	11	10	91	29	10
	F ₂	86	20	14	13	93	41	
		118*						
	F ₃	121	0	13	10	77	30	
522	F ₁	0	40	13	11	85	40	15
		20*						
	F ₁	25	0	13	9	69	40	
412	F ₁	0	66	15	10	67	30	15
		19*						
	F ₁	21	0	13	10	77	25	
590	F ₁	0	30	12	10	83	38	20
		28*						
	F ₁	33	0	11	8	72	37	
	F ₁	50	54	11	9	82	35	10
	F ₂	90	20	13	11	85	36	
		123*						
	F ₂	125	0	13	12	92	28	

* Injected.

normal during the interval of apnea. In order to obtain blood samples from the umbilical vein, the uterus was opened through a small incision and fetuses were extruded into the saline bath, the umbilical circulation remaining intact. The fetuses remained submerged beneath the surface of the bath so that no air entered the respiratory tract. The oxygen content, carbon dioxide content (11) and hemoglobin concentration (12) were determined in blood samples of 0.25 cc. from the umbilical vein. The oxygen capacity of the blood was calculated from the hemoglobin values.

Observations were made on seven fetuses obtained from four litters at term in which rhythmical respiratory movements were abruptly interrupted and apnea

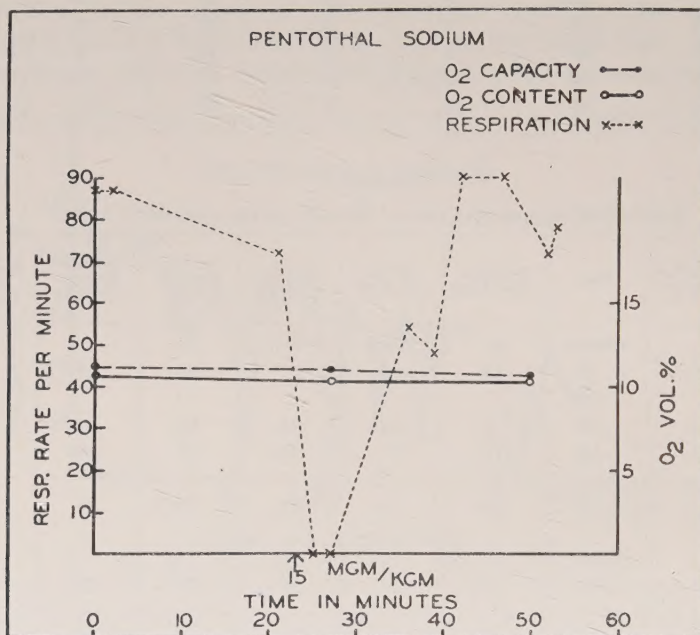


FIG. 3. Anesthetic apnea. In a full-term fetus breathing rhythmically, apnea promptly followed injection of mother with pentothal sodium, 15 mg./kg. at rate of 17 mg./kg. per minute. Blood samples from the umbilical vein before, during and after apnea showed absence of anoxemia. Rabbit No. 516.

occurred following injection of 10 to 20 mg./kg. of pentothal sodium into the maternal ear vein (table 3). Umbilical vein blood samples were taken before, during, and after the fetal anesthetic apnea. No evidence of anoxemia was observed (fig. 3).

The oxygen content of the blood of fetuses during the apnea which followed the administration of pentothal sodium was 8 to 12 volumes per 100 cc. of blood, and the oxygen saturation was 69 to 92 per cent. In blood obtained about one-half hour preceding the injection of pentothal sodium, while the fetuses were showing rhythmical respiratory movements at a rate of 20 to 86 per minute, the oxygen content was 10 to 13 volumes per 100 cc. of blood, and the oxygen saturation of the blood was 67 to 93 per cent. In two fetuses, a third blood sample was ob-

tained following recovery from apnea at 17 and 23 minutes after injection when the respiratory rate was 54 and 72 per minute respectively. In the latter samples the oxygen content was 9 and 10 volumes per 100 cc. of blood, and the oxygen saturation was 82 and 91 per cent.

There was no evidence that the carbon dioxide content of the blood in these experiments was related to apnea of the fetus.

DISCUSSION. The widespread use of barbiturates during the first stage of labor has prompted numerous attempts to evaluate the effects of these drugs upon mother and child (1, 2, 3, 4). Many factors, such as trauma, anoxemia, and anesthetics, complicate passage through the birth canal and may result in injury of the fetus. It has been difficult to isolate the factor of anesthesia under clinical conditions and to determine the role of barbiturates in the pathogenesis of respiratory failure at birth.

In the present experiments full-term fetuses were under direct observation before the onset of labor, in contrast to clinical studies based upon the state of the fetus following delivery. The changes in rate of intrauterine respiratory movements afforded a means of measuring the effect of pentobarbital sodium and pentothal sodium upon the fetus. Likewise, the responses of the maternal animal were determined readily at frequent intervals following various doses of the drugs (10). No general anesthetic was given, since exposure of the uterus was carried out by laparotomy following section of the lumbar spinal cord under procaine anesthesia.

Under such favorable experimental conditions, it was found that 20 mg./kg. of pentobarbital sodium strikingly decreased fetal respiratory activity, while 30 mg./kg. resulted in prolonged respiratory depression. In the case of pentothal sodium, whose effect is known to be much briefer, 10 mg./kg. markedly reduced the rate of fetal respiration; however, after a dosage of 3 to 5 times this amount, fetal respiratory movements returned to normal within the experimental period.

In attempting to correlate the response to pentobarbital sodium in man and in the rabbit, it is of interest to note that the basal metabolic rate of the rabbit is 3 times greater than that of man, the oxygen consumption per kilogram per hour at best being about 200 cc. in man in contrast to 650 cc. in the rabbit (5). Thus, a total dose of 7 grains of pentobarbital sodium in a man of 70 kilograms amounts to 6.5 mg./kg. or, if multiplied by 3, is equal to the dose which resulted in marked depression of the fetal respiratory system in the rabbit when administered intravenously. In the case of pentothal sodium in a man of 70 kilograms, a total dose of 4 grains amounts to 3.7 mg./kg. or, if multiplied by 3, is equal to the dose which caused marked depression of fetal respiration in the rabbit when given intravenously at the rate of 17 mg./kg. per minute.

Pentothal sodium, because of its prompt action as an anesthetic and its rapid inactivation in the body, was favorable for investigating the nature of anesthetic apnea. The three types of apnea, namely, anoxemic, acapnic and anesthetic, may be induced experimentally in fetuses showing rhythmical respiratory movements (8). In the present experiments it was demonstrated that the apnea which followed injection of pentothal sodium was caused by the anesthetic agent rather

than by anoxemia or acapnia. Blood samples obtained from the umbilical vein during the interval of apnea, as well as before and after it, were normal. Furthermore, the abrupt onset of fetal apnea and the recurrence of regular respiratory movements were clearly parallel to the administration of the drug and the rate of its inactivation in the body. Thus, in the absence of anoxemia, fetal apnea occurred promptly following intravenous anesthesia; in contrast, in the absence of any anesthetic agent, as previous experiments have shown (9), sudden oxygen want resulted in prompt interruption of rhythmical fetal respiratory movements. Both types of apnea, anesthetic and anoxemic, may be transient and easily reversible under experimental conditions.

Finally, it may be pointed out that a complete assay of the action of pentobarbital and pentothal in obstetrical analgesia must include not only observation of the direct effect of the drugs upon the fetus but also determination of the effect upon the maternal organism during labor. The methods of analysis and results in the case of morphine have been described previously (7).

CONCLUSIONS

The effect upon the full-term rabbit fetus of various amounts of pentobarbital sodium and pentothal sodium and determined by the changes in rate of fetal respiratory movements following intravenous injection into the maternal animal.

1. Pentobarbital sodium in doses of 5 or 10 mg./kg. resulted in decrease of respiratory rate for less than 15 minutes; 20 mg./kg. resulted in depression of the fetal respiratory rate to about one-third of the initial level for about one-half hour; 30 mg./kg. deeply depressed or abolished fetal respiration for the duration of the experiment.

Following a dose of 20 mg./kg., there was no marked analgesia in the maternal animal.

2. Pentothal sodium, in doses of 10 mg./kg., decreased the fetal respiratory rate to one-third the initial level for about 5 minutes; after a total dosage of 30 to 55 mg./kg., relatively little cumulative effect upon the fetuses was noted.

Following 10 mg./kg., there was no deep analgesia in the maternal animal.

3. Fetal apnea following injection of pentothal sodium was caused by the drug and was not due to anoxemia since analyses of fetal blood showed that the oxygenation and carbon dioxide content remained normal.

Acknowledgement is made of a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago which aided the investigation.

BIBLIOGRAPHY

- (1) BOURNE, W., AND PAULY, A. J., Thiobarbiturates in obstetrics: pentothal and thioethamyl. *Canad. M. A. J.*, **40**: 437, 1939.
- (2) DILLE, J. M., Placental transmission of non-anesthetic doses of barbitol. *Amer. Jr. Obs. and Gyn.*, **32**: 328, 1936.
- (3) GALLOWAY, C. E., GRIER, R. M., AND BLESSING, R., Pentobarbital sodium and scopolamine hydrobromide. *Jr. A. M. A.*, **107**: 1707, 1936.

- (4) IRVING, F. C., BERMAN, S., AND NELSON, H. B., The barbiturates and other hypnotics in labor. *Surg., Gyn. and Obs.*, **58**: 1, 1934.
- (5) KROGH, A., *The Comparative Physiology of Respiratory Mechanisms*. Philadelphia. Univ. Penn. Press, p. 4, 1941.
- (6) ROSENFELD, M., AND SNYDER, F. F., The factor of anesthesia in the pathogenesis of asphyxia neonatorum. *Am. J. Obst. and Gyn.*, **38**: 424, 1939.
- (7) SNYDER, F. F., AND GEILING, E. M. K., The action of morphine in obstetrical analgesia. *Am. Jr. Obs. and Gyn.*, **45**: 604, 1943.
- (8) SNYDER, F. F., AND ROSENFELD, M., Direct observation of intrauterine respiratory movements of the fetus and the rôle of carbon dioxide and oxygen in their regulation. *Am. J. Physiol.*, **119**: 153, 1938.
- (9) SNYDER, F. F., The oxygenation and carbon dioxide content of fetal blood during the interruption of fetal respiration coincident with the breathing of low oxygen mixtures by the maternal animal. *Am. J. Physiol.*, 1943 (in press).
- (10) TATUM, A. L., The present status of the barbiturate problem. *Physiol. Rev.*, **19**: 472, 1939.
- (11) VAN SLYKE, D. D., AND NEILL, J. M., The determination of gases in blood and other solutions by vacuum extraction and manometer measurement. *J. B. C.*, **61**: 523, 1924.
- (12) PETERS AND VAN SLYKE: *Quant. Clin. Chem.*, Vol. II, 668 (Newcomer method).

